PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 217/26, A61K 31/47, C07D 405/06, 405/12 | A1

(11) International Publication Number: **WO 98/47877**

(43) International Publication Date: 29 October 1998 (29.10.98)

(21) International Application Number: PCT/EP98/02244

(22) International Filing Date: 20 April 1998 (20.04.98)

(30) Priority Data:
9708119.4 22 April 1997 (22.04.97) GB

(71) Applicant *(for all designated States except US)*: GLAXO GROUP LIMITED [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: DAUGAN, Alain, Claude-Marie [FR/FR]; Laboratoires Glaxo, Centre de Recherches, Z.A. de Courtaboeuf, 25, avenue de Québec, F-91940 Les Ulis (FR). PIANETTI, Pascal, Maurice, Charles [FR/US]; Glaxo Wellcome Inc., Five Moore Drive, Research Triangle Park, NC 27709 (US).

(74) Agent: LEAROYD, Stephanie, Anne; Glaxo Wellcome plc, Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published

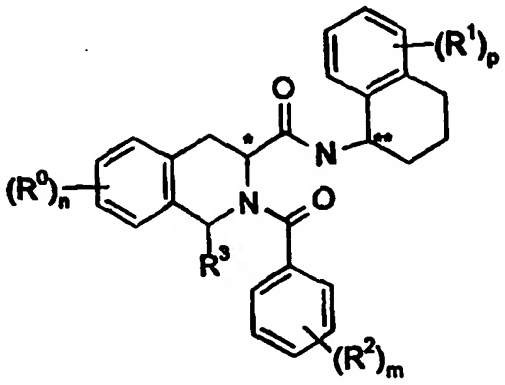
With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

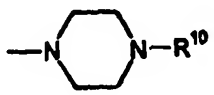
(54) Title: 2-BENZOYL-1,2,3,4-TETRAHYDROISOQUINOLINE-3-CARBOXAMIDE DERIVATIVES AND THEIR USE AS INHIBITORS OF HEPATIC PRODUCTION OF APOB-100

(57) **Abstract**

The present invention relates to a compound of formula (I), wherein R^0 représents hydrogen, halogen, C_{1-4}alkyl, C_{1-4}alkoxy or a methylenedioxy group, and n represents an integer from 1-4; R^1 represents hydrogen, halogen, C_{1-4}alkyl, C_{1-4}alkoxy, trifluoromethoxy or a methylenedioxy group, and p represents an integer from 1-4; R^2 represents one or more groups selected from hydrogen, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, a methylenedioxy group, NR^4R^5, $-(C_{1-4}alkylene)-NR^6R^7$, $-NR^4-$ or $-O-(C_{1-4}$ alkylene$)-NR^8R^9$, 4-morpholino, or formula (II), and m represents an integer from 1-4; R^3 represents hydrogen or C_{1-4} alkyl; R^4-R_{10} independently represent hydrogen or C_{1-4} alkyl; or a pharmaceutically acceptable salt or solvate thereof, to processes for their preparation; and their use in the treatment of conditions mediated by ApoB-100 regulation.



(I)



(II)

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

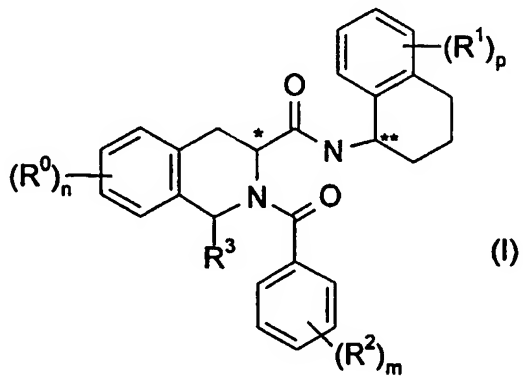
AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

2-BENZOYL-1,2,3,4-TETRAHYDROISOQUINOLINE-3-CARBOXAMIDE DERIVATIVES AND THEIR USE AS INHIBITORS OF HEPATIC PRODUCTION OF APOB-100

This invention relates to novel compounds which inhibit hepatic production of apoprotein B-100 (apoB-100), and to processes for their preparation, pharmaceutical compositions containing them and their medical use. More particularly, the invention relates to novel 1,2,3,4-tetrahydroisoquinolines and their use in therapy. Certain tetrahydroisoquinolines with a therapeutic utility have been described in WO9800403.

ApoB-100 is the main protein component of low density lipoprotein-cholesterol (LDL-C). High LDL-C plasmatic levels are a major risk factor for atherosclerosis and coronary artery diseases. ApoB-100 plasmatic levels correlate with LDL-C plasmatic levels and also constitute a cardiovascular risk factor in themselves. ApoB-100 is exclusively produced by hepatocytes and reducing hepatic production of ApoB-100 should induce a decrease of LDL-C plasmatic levels. Compounds which act as inhibitors of ApoB-100 have been described in PCT.EP97.05636.

The present invention provides a compound of formula (I)



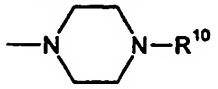
(I)

wherein

R^0 represents hydrogen, halogen, C_{1-4}alkyl, C_{1-4}alkoxy or a methylenedioxy group, and n represents an integer from 1-4;

R^1 represents hydrogen, halogen, C_{1-4}alkyl, C_{1-4}alkoxy, trifluoromethoxy or a methylenedioxy group, and p represents an integer from 1-4;

R^2 represents one or more groups selected from hydrogen, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, a methylenedioxy group,NR^4R^5, -(C_{1-4}alkylene)-NR^6R^7, -NR^4- or -O-(C_{1-4} alkylene)-NR^8R^9, 4-morpholino,

or  , and m represents an integer from 1-4;

R^3 represents hydrogen or C_{1-4} alkyl;

R^4-R^{10} independently represent hydrogen or C_{1-4} alkyl;

or a pharmaceutically acceptable salt or solvate thereof.

Suitable pharmaceutically acceptable salts of the compounds of general formula (I) include acid addition salts formed with pharmaceutically acceptable inorganic acids for example, hydrochlorides, hydrobromides, or sulphates.

The solvates may, for example, be hydrates.

References hereinafter to a compound according to the invention include both compounds of formula (I) and their pharmaceutically acceptable salts together with pharmaceutically acceptable solvates.

It will be appreciated by those skilled in the art that the compounds of formula (I) contain at least two chiral centres (shown as * and ** in formula (I)). The compounds of formula (I) are preferably in their (R) form at centre * . At centre **, the compounds of formula (I) are preferably in the form which is obtained from use of a (+)-1,2,3,4-tetrahydro-1-naphthalenamine intermediate.

Referring to the general formula (I), alkyl and alkylene includes both straight and branched chain saturated hydrocarbon groups. Examples of alkyl groups include methyl, ethyl, isopropyl and tert-butyl groups, and examples of alkylene groups include methylene, ethylene, isopropylene and tert-butylene groups.

Referring to general formula (I), a halogen atom may be a fluorine, chlorine, bromine or iodine atom.

Referring to general formula (I), a methylenedioxy group indicates a -O-CH_2-O-

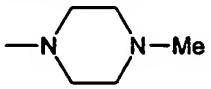
group attached to adjacent carbons on an aromatic ring.

R^0 is suitably a hydrogen, methoxy or methylenedioxy group and n is suitably 1.

R^0 is suitably substituted in either the 6- or 7- position of the bicyclic ring, or where R^0 is methylenedioxy, in the 6- and 7- positions of the ring. R^0 is preferably hydrogen.

R^1 is suitably hydrogen, C_{1-4} alkyl, e.g methyl or isopropyl, halogen, e.g fluorine or chlorine, methoxy or trifluoromethoxy, and p is suitably 1, 2 or 3. Suitably, R^1 is substituted on any one, two or three of the 3-, 4-, 5-, 6- , 7- and 8- positions of the bicyclic ring, including gem substitution where appropriate. R^1 is preferably methyl, methoxy or isopropyl substituted in the 7- position of the bicyclic ring. R^1 is most preferably isopropyl substituted in the 7- position of the bicyclic ring.

R^2 is suitably hydrogen, C_{1-4} alkyl, e.g methyl, halogen, e.g. chlorine, methoxy, methylenedioxy, NMe_2, -O-(C_{1-4}alkylene)-NR^6R^7, e.g. 2-dimethylamino-ethoxy, 2-dimethylamino-propoxy, 2-dimethylamino-1-methyl-ethoxy, 2-dimethylamino-2-methyl-propoxy or 2-dimethylamino-1,1-dimethyl-ethoxy, 4-morpholino

or  , and m is suitably 1, 2 or 3.

Suitably, R^2 is mono-, di- or tri- substituted on the 2-, 3- or 4- positions of the phenyl ring, or where R^2 is methylendioxy, on the 3- and 4- positions of the phenyl ring. Preferably, R^2 is mono-substituted on the 3- position of the phenyl ring.

Preferably, R^2 is methyl, dimethylamino or 4-morpholino.

Most preferably, R^2 is 2-dimethylamino-ethoxy substituted in the 3-position of the phenyl ring.

R^3 is suitably hydrogen.

Suitable compounds according to the invention include:
2-(4-Methyl benzoyl)-N-(7-methyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-(3-Dimethylamino-4-methyl benzoyl)-N-(7-methyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-(3-Dimethylamino benzoyl)-N-(7-methyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-(3-(Morpholin-4-yl)benzoyl)-N-(7-methyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-(3-(Morpholin-4-yl)benzoyl)- N-(7-methoxy-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-(3-Dimethylamino benzoyl)-N-(7-methoxy-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-[3-(2-Dimethylamino-ethoxy)-benzoyl]-N-(7-isopropyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-[3-(2-Dimethylamino-ethoxy)-benzoyl]-N-(7-methyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-[3-(2-Dimethylamino-ethoxy)-benzoyl]-N-(5,7-dimethyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-(4-Methyl-benzoyl)-N-(7-isopropyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-(3,4-Methylenedioxy-benzoyl)-N-(7-methyl-1,2,3,4-tetrahydro-naphthalen -1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-(3-Morpholin-4-yl-benzoyl)-N-(7-isopropyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-[3-(2-Diethylamino-ethoxy)-benzoyl]-N-(7-isopropyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-(3-Morpholin-4-yl-benzoyl)-N-(7-tert-butyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-[3-(2-Dimethylamino-ethoxy)-benzoyl]-N-(7-tert-butyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-[3-(3-Dimethylamino-propoxy)-benzoyl]-N-(7-isopropyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-[3-(2-Diisopropylamino-ethoxy)-benzoyl]-N-(7-isopropyl-1,2,3,4-tetrahydro-

naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-(4-Methyl-benzoyl)-N-(6,7-methylenedioxy-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-(3-Morpholin-4-yl-benzoyl)-N-(6,7-methylenedioxy-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-(4-Methyl-benzoyl)-N-(5,7-dimethyl-1,2,3,4-tetrahydro-naphthalen -1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-(4-Methyl-benzoyl)-N-(6-fluoro-7-methoxy-1,2,3,4-tetrahydro-naphthalen -1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-(3-Methoxy-benzoyl)-N-(7-methyl-1,2,3,4-tetrahydro-naphthalen -1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-[3-(4-Methyl-piperazin-1-yl)-benzoyl]-N-(7-methoxy-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-(3-Dimethylamino-4-methoxy-benzoyl)-N-(7-methyl-1,2,3,4-tetrahydro-naphthalen -1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-(4-Chloro-benzoyl)-N-(7-methyl-1,2,3,4-tetrahydro-naphthalen -1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-(3-Morpholin-4-yl-benzoyl)-N-(1,2,3,4-tetrahydro-naphthalen -1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-(2-Dimethylamino-benzoyl)-N-(1,2,3,4-tetrahydro-naphthalen -1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-(3-Morpholin-4-yl-benzoyl)-N-(4,4,7-trimethyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-(3-Morpholin-4-yl-benzoyl)-N-(4,4,6-trimethyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-(3-Morpholin-4-yl-benzoyl)-N-(7-methoxy-4,4-dimethyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-(3-Morpholin-4-yl-benzoyl)-N-(3,3-dimethyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide isomer 1;
2-(3-Dimethylamino-benzoyl)-N-(7-methoxy-4,4-dimethyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-(3-Morpholin-4-yl-benzoyl)-N-(5,7-dimethyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-(3-Morpholin-4-yl-benzoyl)-N-(7-trifluoromethoxy-1,2,3,4-tetrahydro-

naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-(3-Morpholin-4-yl-benzoyl)-N-(7-fluoro-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-[3-(2-dimethylamino-2-methyl-propoxy)-benzoyl]-N-(7-isopropyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-[3-(2-dimethylamino-1,1-dimethyl-ethoxy)-benzoyl]-N-(7-isopropyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
or a pharmaceutically acceptable salt or solvate thereof.

Preferred compounds of the invention include:
2-[3-(2-dimethylamino-ethoxy)-benzoyl]-N-(7-isopropyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-[3-(2-Dimethylamino-ethoxy)-benzoyl]-N-(7-methyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-[3-(2-Dimethylamino-ethoxy)-benzoyl]-N-(5,7-dimethyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-(4-Methyl-benzoyl)-N-(7-isopropyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-(3,4-Methylenedioxy-benzoyl)-N-(7-methyl-1,2,3,4-tetrahydro-naphthalen -1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-(3-Morpholin-4-yl-benzoyl)-N-(7-isopropyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-[3-(2-Diethylamino-ethoxy)-benzoyl]-N-(7-isopropyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-(3-Morpholin-4-yl-benzoyl)-N-(7-tert-butyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-[3-(2-Dimethylamino-ethoxy)-benzoyl]-N-(7-tert-butyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-[3-(3-Dimethylamino-propoxy)-benzoyl]-N-(7-isopropyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-[3-(2-Diisopropylamino-ethoxy)-benzoyl]-N-(7-isopropyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-[3-(2-dimethylamino-propoxy)-benzoyl]-N-(7-isopropyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;

2-[3-(2-dimethylamino-1-methyl-ethoxy)-benzoyl]-N-(7-isopropyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
or a pharmaceutically acceptable salt or solvate thereof.

Particularly preferred compounds of the invention include 2-[3-(2-dimethylamino-ethoxy)-benzoyl]-N-(7-isopropyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
or a pharmaceutically acceptable salt or solvate thereof.

The compounds of the invention are inhibitors of hepatic production of apoB-100 and are thus of use in the treatment of conditions resulting from elevated circulating levels of apoB-100.

The ability of the compounds of the invention to inhibit the production of apoB-100 by human hepatocytes in vitro is determined using a human hepatocarcinoma cell line, Hep G_2, as a model system. The specificity of the compounds of the invention is established by comparing the effects on apoB-100, apoprotein A-1, and fibrinogen production. A specificity of at least 100 is preferred.

The in vivo profile of the compounds was determined by acute oral administration of the compounds of the invention to DBA/2 mice and Wistar rats with measurement of apoB-100 plasmatic levels as percentage of control values. Active compounds are further evaluated in Wistar rats by repeated oral administration (once a day) with measurement of total cholesterol, low density lipoprotein-cholesterol, triglycerides, apoB-100 and apoA-I plasmatic levels as a percentage of control values.

The compounds of the invention are potent and specific inhibitors of hepatic production of apoB-100, which furthermore exhibit good oral bioavailability and duration of action.

Compounds of the invention are of use in the treatment of atherosclerosis, pancreatitis, non-insulin dependent diabetes mellitus (NIDDM), and coronary

heart diseases.

Compounds of the invention are also useful in lowering serum lipid levels, cholesterol and/or triglycerides, and are of use in the treatment of hyperlipemia, hyperlipidemia, hyperlipoproteinemia, hypercholesterolemia and/or hypertriglyceridemia.

The invention therefore provides a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof for use in therapy, in particular in human medicine.

There is also provided as a further aspect of the invention the use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof in the preparation of a medicament for use in the treatment of conditions resulting from elevated circulating levels of apoB-100.

In an alternative or further aspect there is provided a method for the treatment of a mammal, including man, in particular in the treatment of conditions resulting from elevated circulating levels of apoB-100, comprising administration of an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

It will be appreciated that reference to treatment is intended to include prophylaxis as well as the alleviation of established symptoms. Compounds of formula (I) may be administered as the raw chemical but the active ingredient is preferably presented as a pharmaceutical formulation.

Accordingly, the invention also provides a pharmaceutical composition which comprises at least one compound of formula (I) or a pharmaceutically acceptable salt thereof and formulated for administration by any convenient route. Such compositions are preferably in a form adapted for use in medicine, in particular human medicine, and can conveniently be formulated in a conventional manner using one or more pharmaceutically acceptable carriers or excipients.

Thus compounds of formula (I) may be formulated for oral, buccal, parenteral, transdermal, topical (including ophthalmic and nasal), depot or rectal administration or in a form suitable for administration by inhalation or insufflation (either through the mouth or nose).

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the composition may take the form of tablets or lozenges formulated in conventional manner.

For transdermal administration the compounds according to the invention may be formulated as creams, gels, ointments or lotions or as a transdermal patch. Such compositions may for example be formulated with an aqueous or oily base

with the addition of suitable thickening, gelling, emulsifying, stabilising, dispersing, suspending, and/or colouring agents.

The compounds of the invention may be formulated for parenteral administration by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The compounds of the invention may be formulated for topical administration in the form of ointments, creams, gels, lotions, pessaries, aerosols or drops (e.g. eye, ear or nose drops). Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Ointments for administration to the eye may be manufactured in a sterile manner using sterilised components.

Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents. Drops may be formulated with an aqueous or non aqueous base also comprising one or more dispersing agents, stabilising agents, solubilising agents or suspending agents. They may also contain a preservative.

The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

The compounds of the invention may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable

polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

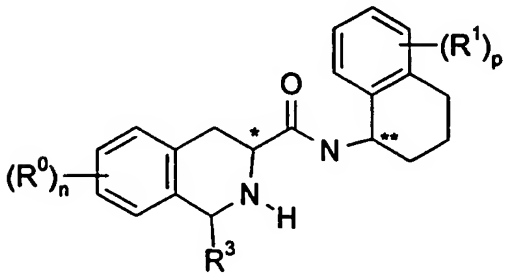
For intranasal administration, the compounds of the invention may be formulated as solutions for administration via a suitable metered or unit dose device or alternatively as a powder mix with a suitable carrier for administration using a suitable delivery device.

The compositions may contain from 0.1% upwards, e.g. 0.1 - 99% of the active material, depending on the method of administration. A proposed dose of the compounds of the invention is 0.25mg/kg to about 125mg/kg bodyweight per day e.g. 20mg/kg to 100mg/kg per day. It will be appreciated that it may be necessary to make routine variations to the dosage, depending on the age and condition of the patient and the precise dosage will be ultimately at the discretion of the attendant physician or veterinarian. The dosage will also depend on the route of administration and the particular compound selected.

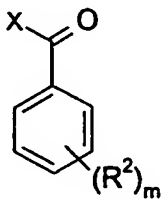
The compounds of formula (I) may, if desired, be administered with one or more therapeutic agents and formulated for administration by any convenient route in a conventional manner. Appropriate doses will be readily appreciated by those skilled in the art. For example, the compounds of formula (I) may be administered in combination withp an HMG CoA reductase inhibitor or an agent for inhibition of bile acid transport.

Compounds of formula (I), and salts and solvates thereof, may be prepared by the general methods outlined hereafter. In the following description, the groups R^0, R^1, R^2 and R^3 are as previously defined for compounds of formula (I).

According to a general process, a compound of formula (I) may be prepared by reacting a compound of formula (II) with a compound of formula (III)



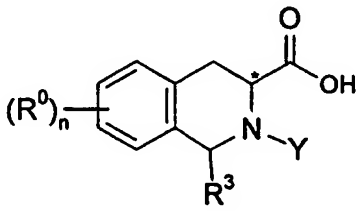
(II)



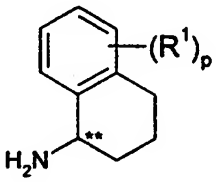
(III)

where X represents a suitable halide leaving group, e.g. chloride, or X represents a hydroxy group. The reaction is conveniently carried out under standard coupling conditions for acid or acid halide couplings with amines.

A compound of formula (II) may be prepared by reaction of a compound of formula (IV) with a compound of formula (V)



(IV)



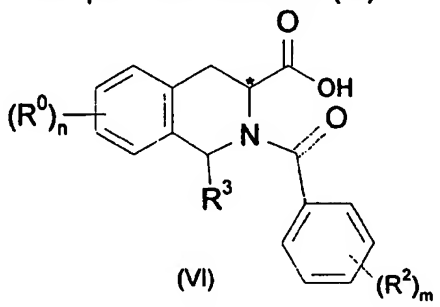
(V)

where Y is a suitable amine protecting group, e.g. tert-butoxycarbonyl (Boc), under standard coupling conditions for an acid/amine coupling, followed by deprotection of the protecting group under suitable conditions.

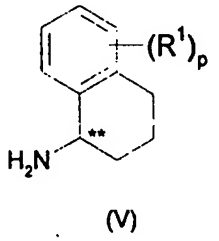
The various general methods described above may be useful for the introduction of the desired groups at any stage in the stepwise formation of the required compound, and it will be appreciated that these general methods can be combined in different ways in such multi-stage processes. The sequence of the reactions in multi-stage processes should of course be chosen so that the

reaction conditions used do not affect groups in the molecule which are desired in the final product.

Thus, according to a second method, compounds of formula (I) may be prepared by reaction of compounds of formula (VI) and compounds of formula (V)



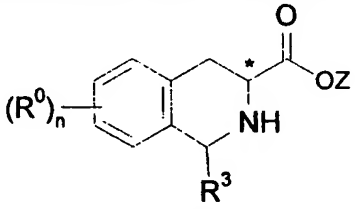
(VI)



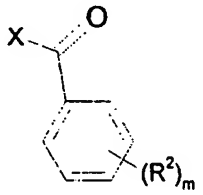
(V)

under standard conditions for amine and acid couplings.

Compounds of formula (VI) may be prepared by reaction of compounds of formula (VII) with compounds of formula (III)



(VII)



(III)

where Z is a suitable C_{1-4} alkyl protecting group, e.g. methyl, and X is OH, under standard conditions for acid and amine couplings, followed by removal of the acid protecting group.

It will be appreciated that certain intermediates, e.g. compounds of formula (II) and (VI), are novel and may, therefore, provide a further aspect of the present invention. Compounds of formula (III), (IV), (V) and (VII) are known or may be prepared by standard methods.

Pharmaceutically acceptable salts may also be prepared from other salts, including other pharmaceutically acceptable salts, of the compound of formula (I) using conventional methods.

The compounds of formula (I) may readily be isolated in association with solvent molecules by crystallisation from or evaporation of an appropriate solvent to give the corresponding solvates.

When a specific enantiomer of a compound of general formula (I) is required, this may be obtained for example by resolution of a corresponding enantiomeric mixture of a compound of formula (I) using conventional methods.

Thus, in one example an appropriate optically active acid may be used to form salts with the enantiomeric mixture of a compound of general formula (I). The resulting mixture of isomeric salts may be separated, for example, by fractional crystallisation into the diastereoisomeric salts from which the required enantiomer of a compound of general formula (I) may be isolated by conversion into the required free base.

Alternatively, enantiomers of a compound of general formula (I) may be synthesised from the appropriate optically active intermediates using any of the general processes described herein.

The invention is further illustrated by the following intermediates and examples. All temperatures are in degrees centigrade.

Intermediate 1

(+)-7-Methyl-1,2,3,4-tetrahydro-naphthalen-1-ylamine

To a solution of racemic 7-methyl-1,2,3,4-tetrahydro-naphthalen-1-ylamine (12.1 g) in methanol (70 mL) was added a solution (L)-(+)-tartaric acid (11.2 g) in methanol (70 mL) and the resulting solution was kept overnight at room temperature. The crystalline salt was filtered off and dried to give the tartrate salt (9.7g) as white crystals (m.p.: 189-191°C). The salt was treated with 1N aqueous NaOH, extracted with diethyl ether and the resulting organic phase was dried over sodium sulphate, filtered and evaporated under reduced pressure to give the title compound as a pale yellow liquid (4.7 g).

$[\alpha]_D$ = +46.8° (c = 0.5; $CHCl_3$)

Intermediate 2

(+)-7-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylamine

To a stirred suspension of racemic 7-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylamine (20 g) in water (80 mL) was added (L)-(+)-tartaric acid (16.9 g) and the resulting suspension was warmed to effect complete solution. After 3 hours at room temperature, the crystalline salt was filtered off and then recrystallised twice from methanol to give the tartrate salt (8 g) as white crystals (m.p.: 211-212°C). The salt (1g) was treated with 1N aqueous NaOH, extracted with diethyl ether, and the resulting organic phase was dried over sodium sulphate, filtered and evaporated under reduced pressure to give the title compound as a pale yellow liquid (0.5 g).

$[\alpha]_D$ = +45.9° (c = 1.12; MeOH)

Intermediate 3

3-Dimethylamino-4-methyl benzoic acid methyl ester

To a stirred suspension of 3-amino-4-methyl benzoic acid methyl ester (6.6 g) in methanol (60 mL) was added a 37% aqueous formaldehyde solution (8 mL) and 10% palladium on charcoal (0.66 g) and the mixture was stirred under hydrogen atmospher for 16 hours at room temperature. The catalyst was filtered off, the filtrate was evaporated under reduced pressure and the residue was then purified by chromatography eluting with dichloromethane/ethyl acetate (90/10) to give the title compound as a colourless liquid (6.7 g).

GC/MS (EI, 70 eV): m/z = 193

Intermediate 4

3-Dimethylamino-4-methyl benzoic acid

A 1N solution of NaOH (48.9 mL) was added to a solution of 3-dimethylamino-4-methyl benzoic acid methyl ester (6.3 g) in methanol (60 mL) and the solution was stirred at room temperature for 16 hours. The reaction mixture was evaporated under reduced pressure and 1N HCl (48.9 mL) was added. The aqueous layer was extracted with dichloromethane and the organic phase was washed with brine, dried over sodium sulphate and evaporated. The white solid obtained was recrystallised from hexane to give the title compound as white

crystals (5g).
m.p.: 131-133°C.

Intermediate 5
2-(tert-Butoxycarbonyl)-N-(7-methyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide
To a solution of (+)-7-methyl-1,2,3,4-tetrahydro-naphthalen-1-ylamine (4.8 g) in dichloromethane (100 mL) were added Boc-D-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (8.24 g), 1-hydroxybenzotriazole (5.21 g) and triethylamine (3.86 g). The mixture was cooled at 0°C and treated with 1-(3-dimethylamino propyl)-3-ethylcarbodiimide hydrochloride (7.37 g) followed by stirring for 3 hours at room temperature. The reaction mixture was washed successively with water, 1N HCl, an aqueous solution of $NaHCO_3$ and brine, and then was dried over sodium sulphate and evaporated. The oily residue was crystallised from diisopropyl ether to give the title compound as white crystals (9.7 g).
m.p.:140-142°C.

Similarly prepared was:
Intermediate 6
2-(tert-Butoxycarbonyl)-N-(7-methoxy-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide as white crystals (16g),
m.p.:149-151°C
from (+)-7-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylamine (8.5 g), and Boc-D-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (13.3g).

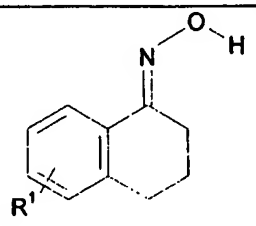
Intermediate 7
N-(7-methyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide
To a stirred solution of 2-(tert-butoxycarbonyl)-N-(7-methyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (intermediate 5) (9.7 g) in anhydrous dichloromethane (70 mL) cooled at 0°C was added trifluoroacetic acid (32 mL) and the solution was allowed to react at room temperature. After 4 hours, the reaction mixture was evaporated to dryness under reduced pressure and the residue was taken up in water, basified with a

saturated aqueous solution of $NaHCO_3$ and extracted with dichloromethane. The resulting organic phase was washed with brine, dried over sodium sulphate, filtered and evaporated to dryness. The white solid obtained was recrystallised from diisopropyl ether to give the title compound as white crystals (6.7 g).
m.p.: 132-134°C.

Similarly prepared was:
Intermediate 8
N-(7-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide as white crystals (11.8 g),
m.p.: 131-133°C
from 2-(tert-butoxycarbonyl)-N-(7-methoxy-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (16 g) (intermediate 6).

Intermediate 9
4,4,7-Trimethyl-3,4-dihydro-2H-naphthalen-1-one oxime
To a solution of 4,4,7-trimethyl-3,4-dihydro-2H-naphthalen-1-one (1.7 g) in ethanol (30 mL) was added a solution of hydroxylamine hydrochloride (1 g) in water (20 mL) and sodium acetate (2.2 g). After 48 hours at room temperature, the solvents are removed under reduced pressure and the residue was taken up in water and extracted with diethyl ether. The organic layer was washed with water, dried over sodium sulfate and evaporated to dryness to give the title compound as an oil (2 g).
GC/MS (EI, 70 eV) : m/z=203 (M^+)

Similarly prepared were:

	Int. No.	R^1	M.P. °C or M/Z
	10	4,4,6-Trimethyl	142-144
	11	3,3-Dimethyl-	131-133

	12	7-Trifluoromethoxy	245 (M^+)

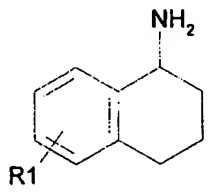
Intermediate 13

7-Methoxy-4,4-dimethyl-1,2,3,4-tetrahydro-naphthalen-1-ylamine hydrochloride

A solution of 7-methoxy-4,4-dimethyl-3,4-dihydro-2H-naphthalen-1-one oxime (3.5 g) in methanol (60 mL) was hydrogenated in the presence of 10% Pd/C (0.3 g) for 16 hours at room temperature. After removal of the catalyst, the solvent was evaporated in vacuo and the residue was dissolved in diethyl ether and treated with a solution of hydrochloric acid in diethyl ether. The precipitate obtained was filtered and washed with diethyl ether to give the title compound as white crystals (3.7 g).

m.p.: 234-236°C.

Similarly prepared were :

	Int. No.	R^1	M.P. °C
	14	4,4,7-Trimethyl	242-243
	15	4,4,6-Trimethyl	>250
	16	3,3-Dimethyl	250
	17	7-Trifluoromethoxy	230-233
	18	6-Fluoro-7-methoxy	>250

Intermediate 19

7-Fluoro-1,2,3,4-tetrahydro-naphthalen-1-ylamine

A solution of 7-fluoro-3,4-dihydro-2H-naphthalen-1-one oxime (0.56 g) in acetic acid (15 mL) was hydrogenated in the presence of 10% Pd/C (0.06 g) for 16 hours at 40°C. After removal of the catalyst, the solvent was evaporated in vacuo and the residue was basified with a solution of sodium hydroxide, and extracted with dichloromethane. The organic layer was washed with brine, dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by flash chromatography eluting with dichloromethane/methanol (90/10) to give the title compound as white crystals (0.07 g).

m.p.: 62-64°C.

Intermediate 20
(7-Isopropyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-(1-phenyl-ethyl)-amine

A solution of 7-isopropyl-3,4-dihydro-2H-naphthalen-1-one (14.5 g), (S)-(-)-α-methyl benzylamine (27.9 g) and a catalytic amount of p-toluenesulfonic acid in toluene (150 mL) was refluxed under a dean-stark trap until conversion was complete (48 hours). The solvent was then evaporated under reduced pressure and the oily residue (22.5 g) was dissolved in methanol (300 mL). The solution was cooled at 0°C and treated portionwise with sodium borohydride (1.8 g) and then stirred for 0.5 hour at the same temperature. Water was then added and the mixture was evaporated to dryness and filtered on silica gel eluting with dichloromethane / methanol (95/5) to give the title compound (20.4 g) as an oil.
GC/MS (EI, 70 eV) : m/z= 293 (M^+)

Similarly prepared was:

Intermediate 21
(7-tert-Butyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-(1-phenyl-ethyl)-amine as an oil (15.2 g),
GC/MS (EI, 70 eV) : m/z= 307 (M^+)
from 7-tert-butyl-3,4-dihydro-2H-naphthalen-1-one (10.1 g) and (S)-(-)- α-methyl benzylamine (18.15 g).

Intermediate 22
(+)-7-Isopropyl-1,2,3,4-tetrahydro-naphthalen-1-ylamine hydrochloride

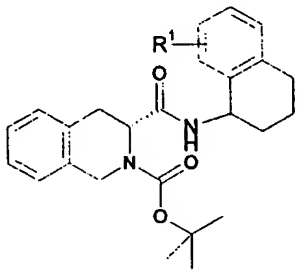
A mixture of (7-isopropyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-(1-phenyl-ethyl)-amine (20.2 g ; 69 mmol), ammonium formate (13 g ; 206 mmol) and 10% Pd/C (1 g) in methanol (300 mL) was refluxed for 3 hours. The reaction mixture was cooled at room temperature, the catalyst was filtered off and the filtrate was evaporated under reduced pressure. The residue was treated with 1N sodium hydroxide , extracted with diethyl ether, and the organic phase was dried over sodium sulfate and filtered. The organic solution was then treated with hydrochloric acid and the precipitate was filtered and dried to give the title

compound (10.5 g) as a white solid.
m.p . : > 250°C
$[\alpha]_D$ = +29.4° (C=0.52 ;MeOH).

Similarly prepared was:

Intermediate 23
(+)-7-tert-butyl-1,2,3,4-tetrahydro-naphthalen-1-ylamine hydrochloride as a white solid (10.2 g),
m.p . : > 250°C
$[\alpha]_D$ = +28° (C=0.58 ;MeOH)
from (7-tert-Butyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-(1-phenyl-ethyl)-amine (15.2 g).

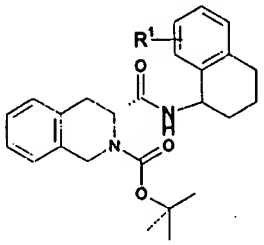
Similarly prepared as Intermediate 5:

	Int. No.	R^1	M.P. °C
	24	7-isopropyl	129-131
	25	7-tert-butyl	60
	26	H	133-135

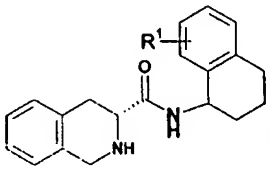
Intermediate 27
2-(tert-Butoxycarbonyl)-N-(5,7-dimethyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide as a mixture of diastereoisomers
To a solution of racemic 5,7-dimethyl-1,2,3,4-tetrahydro-naphthalen-1-ylamine hydrochloride (1.1 g) in dichloromethane (20 mL) were added Boc-D-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (1.4 g), 1-hydroxybenzotriazole (0.9 g) and triethylamine (1.1 g). The mixture was cooled at 0°C and treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.3 g) followed by stirring for 3 hours at room temperature. The reaction mixture was washed

successively with 1N HCl, an aqueous solution of NaHCO3 and brine, and then was dried over sodium sulfate and evaporated. The residue was crystallised from diisopropyl ether to give the title compound (2 g) as white crystals.
m.p.: 152-154°C.

Similarly prepared were :

	Int. No.	R^1	M.P. °C
	28	6,7-methylenedioxy	82
	29	6-fluoro-7-methoxy	150-155

Similarly prepared to Intermediate 7:

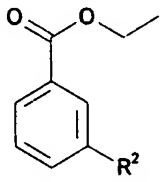
	Int. No.	R^1	M.P. °C
	30	7-isopropyl	115-117
	31	7-tert-Butyl	103-105
	32	H	178-180
	33	5,7-dimethyl (isomer 1)	152-153
	34	5,7-dimethyl (isomer 2)	173-175
	35	6,7-methylenedioxy (isomer 1)	133-135
	36	6,7-methylenedioxy (isomer 2)	175-177
	37	6-fluoro-7-methoxy (isomer 1)	153-155
	38	6-fluoro-7-methoxy (isomer 2)	149-151

Intermediate 39
3-(4-Methyl-piperazin-1-yl)-benzoic acid ethyl ester

A mixture of 3-amino-benzoic acid ethyl ester (19.7 g), bis-(2-chloro-ethyl)-methylamine (23 g) and sodium carbonate (63 g) in butanol (450 mL) was stirred and heated under reflux for 16 hours. The mixture was evaporated under reduced pressure and the residue was taken up in water and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, evaporated under reduced pressure and the residue was purified by flash chromatography eluting with dichloromethane/methanol (95/5) to give the title compound as a pale yellow oil (3.8 g).
GC/MS (EI,70 eV) : m/z=248 (M^+)

Intermediate 40
3-(3-Dimethylamino-propoxy)-benzoic acid ethyl ester
A mixture of 3-hydroxy-benzoic acid ethyl ester (3.32 g), (3-chloro-propyl)-dimethylamine hydrochloride (3.79 g) and anhydrous potassium carbonate (6.62 g) in acetone (150 mL) was stirred and heated under reflux for 24 hours. It was then cooled, and the solid material was filtered off and washed with acetone. The filtrate was evaporated under reduced pressure and the residue was purified by flash chromatography eluting with dichloromethane/methanol (95/5) to give the title compound (4 g) as a pale yellow oil.
GC/MS (EI,70 eV) : m/z=251 (M^+)

Similarly prepared were :

	Int. No.	R^2	M/Z
	41	2-Dimethylamino-ethoxy	237 (M^+)
	42	2-Diisopropylamino-ethoxy	293 (M^+)

Intermediate 43
3-(2-dimethylamino-1-methyl-ethoxy)-benzoic acid ethyl ester and 3-(2-dimethylamino-propoxy)-benzoic acid ethyl ester
A mixture of 3-hydroxy-benzoic acid ethyl ester (16.6 g), (2-chloro-propyl)-

dimethylamine hydrochloride (21.6 g) and anhydrous potassium carbonate (41.1 g) in acetone (400 mL) was stirred and heated under reflux for 16 hours. It was then cooled, and the solid material was filtered off and washed with acetone. The filtrate was evaporated under reduced pressure and the residue was purified by flash chromatography eluting with dichloromethane/methanol (95/5) to give first 3-(2-dimethylamino-1-methyl-ethoxy)-benzoic acid ethyl ester (7 g) as a pale yellow oil,

GC/MS (EI, 70eV) : m/z= 251 (M^+)

followed by 3-(2-dimethylamino-propoxy)-benzoic acid ethyl ester (10 g) as a pale yellow oil,

GC/MS (EI, 70eV) : m/z= 251 (M^+)

Intermediate 44

3-(2-dimethylamino-1,1-dimethyl-ethoxy)-benzoic acid ethyl ester and 3-(2-dimethylamino-2-methyl-propoxy)-benzoic acid ethyl ester

A solution of 3-hydroxy-benzoic acid ethyl ester (1.6 g) in tetrahydrofuran (50 mL) containing triphenyl phosphine (2.9 g) was stirred at room temperature while diethyl azodicarboxylate (1.9 g) was added dropwise. To this solution was added 2-dimethylamino-2-methyl-propan-1-ol (1.2 g) and the mixture was stirred at room temperature for 16 hours. Evaporation of the solvent in vacuo gave an oil which was dissolved in diethyl ether and the organic layer was washed with water, dried over sodium sulfate, evaporated and purified by flash chromatography eluting with dichloromethane/methanol (90/10) to give first : 3-(2-dimethylamino-1,1-dimethyl-ethoxy)-benzoic acid ethyl ester (1.2 g) as a pale yellow oil,

GC/MS (EI,70eV) : m/z= 265 (M^+)

followed by 3-(2-dimethylamino-2-methyl-propoxy)-benzoic acid ethyl ester (0.3 g) as a pale yellow oil,

GC/MS (EI,70eV) : m/z= 265 (M^+)

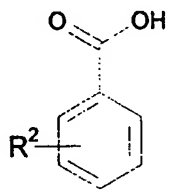
Intermediate 45

3-Morpholin-4-yl-benzoic acid

To a solution of 3-morpholin-4-yl-benzoic acid ethyl ester (6.1 g) in ethanol (40 mL) was added a 1N solution of sodium hydroxide (55 mL) and the mixture was

heated under reflux for 1 hour. Ethanol was then evaporated under reduced pressure and the aqueous solution was extracted with diethyl ether and neutralised with a 1N solution of hydrochloric acid (55 mL). The aqueous layer was then extracted with dichloromethane, and the organic layer was dried over sodium sulfate and evaporated to dryness. The solid obtained was recrystallised from acetonitrile to give the title compound (3.6 g) as white crystals.
m.p. : 168-170°C.

Similarly prepared were :

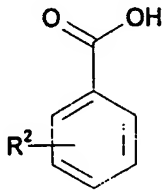
	Int. No.	R^2	M.P. °C
	46	3-Dimethylamino-4-methoxy	150-152
	47	3-(4-Methyl-piperazin-1-yl)	190-192

Intermediate 48

3-(3-Dimethylamino-propoxy)-benzoic acid hydrochloride

To a solution of 3-(3-dimethylamino-propoxy)-benzoic acid ethyl ester (4 g) in ethanol (50 mL) was added a solution of sodium hydroxide (1.3 g) in water (50 mL) and the mixture was heated at 60°C for 1.5 hours. Ethanol was then evaporated under reduced pressure and the solution was acidified with concentrated hydrochloric acid. The aqueous solution was evaporated to dryness and the resulting solid residue was extracted with hot ethanol and the solution was filtered and evaporated. The solid obtained was recrystallised from propanol-2 to give the title compound (3.5 g) as white crystals.
m.p. : 180-182°C.

Similarly prepared were:

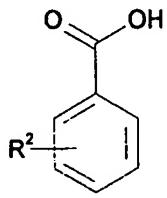
	Int. No.	R^2	M.P. °C
	49	3-(2-dimethylamino-ethoxy)	194-196
	50	3-(2-diethylamino-ethoxy)	127-129
	51	3-(2-diisopropylamino-ethoxy)	199-201

Intermediate 52

3-(2-dimethylamino-propoxy)-benzoic acid hydrochloride

To a solution of 3-(2-dimethylamino-propoxy)-benzoic acid ethyl ester (10 g) in ethanol (100 mL) was added a normal solution of sodium hydroxide (80 mL) and the mixture was heated under reflux for 0.5 hour. Ethanol was then evaporated under reduced pressure and the solution was acidified with concentrated hydrochloric acid. The aqueous solution was evaporated to dryness and the resulting solid residue was extracted with hot ethanol and the solution was filtered and evaporated. The solid obtained was washed with diisopropyl ether to give the title compound (9.5 g) as white crystals.
m.p. : 177-179°C.

Similarly prepared were :

	Int. No.	R^2	M.P. °C
	53	3-(2-dimethylamino-1-methyl-ethoxy)	207-209
	54	3-(2-dimethylamino-2-methyl-propoxy)	200-202
	55	3-(2-dimethylamino-1,1-	217-219

		dimethyl-ethoxy)	

Intermediate 56
(R)-2-(3-Dimethylamino-benzoyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid ethyl ester

To a solution of (R)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid ethyl ester hydrochloride (5.8 g) in dichloromethane (170 mL) were added 3-dimethylamino-benzoic acid (4 g), 1-hydroxy benzotriazole (4.2 g) and triethylamine (5.4 g). The mixture was cooled at 0°C and treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (5.9 g) followed by stirring for 4 hours at room temperature. The reaction mixture was washed successively with water, an aqueous solution of NaHCO3 and brine, and then was dried over sodium sulfate and evaporated. The residue was purified by flash chromatography eluting with dichloromethane/ethyl acetate (90/10) to give the title compound as a yellow oil (6.5 g).

GC/MS(EI, 70eV) : m/z=352 (M^+)

Similarly prepared was :

Intermediate 57
(R)-2-(3-Morpholin-4-yl-benzoyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid ethyl ester as a yellow oil (2.2 g),
GC/MS(EI, 70eV) : m/z=394 (M^+)
from (R)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid ethyl ester hydrochloride (1.8 g) and 3-morpholin-4-yl-benzoic acid (1.6 g).

Intermediate 58
(R)-2-(3-Dimethylamino-benzoyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

A stirred solution of (R)-2-(3-dimethylamino-benzoyl)-1,2,3,4-tetrahydro isoquinoline-3-carboxylic acid ethyl ester (6.5 g) in a mixture of THF, MeOH, H2O (30/10/10 mL) cooled to 5°C, was treated with LiOH.H2O (1.2 g) and the mixture was stirred at the same temperature for 8 hours. The solvents were removed under reduced pressure and the residue was neutralized with 1N HCl,

and extracted with dichloromethane. The organic phase was washed with water, dried over sodium sulfate and evaporated under reduced pressure. The solid obtained was recrystallised from ethyl acetate to give the title compound as white crystals (5 g),
m.p.: 202-204°C.

Similarly prepared was :

Intermediate 59
(R)-2-(3-Morpholin-4-yl-benzoyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid as white crystals (1.7 g)
m.p.: 106-108°C
from (R)-2-(3-morpholin-4-yl-benzoyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid ethyl ester (2.2 g).

Example 1
2-(4-Methyl benzoyl)-N-(7-methyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide
Method A:
To a solution of N-(7-methyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (Intermediate 7) (160 mg) in dichloromethane (8 mL) were added 4-methyl benzoic acid (68 mg), 1-hydroxybenzotriazole (81 mg) and triethylamine (61 mg). The mixture was cooled at 0°C and treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (114 mg) followed by stirring for 16 hours at room temperature. The reaction mixture was diluted with dichloromethane and washed successively with 1N HCl, an aqueous solution of $NaHCO_3$ and brine, and then was dried over sodium sulphate and evaporated. The residue was purified by flash chromatography eluting with dichloromethane/ ethyl acetate (90/10) and crystallised from dichloromethane / hexane to give the title compound as white crystals (150 mg).
m.p.:161-162°C.
$[\alpha]_D$ = + 47.1° (C=1.1 ; $CHCl_3$)
Analysis for $C_{29}H_{30}N_2O_2$ Calculated: C,79.42;H,6.89;N,6.39;

Found: C,79.01;H,7.1;N,6.43%.

Method B

A solution of 4-methyl benzoyl chloride (913 mg) in dry dichloromethane (10 mL) was added dropwise to a solution of N-(7-methyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (Intermediate 7) (1.8 g) and triethylamine (597 mg) while being stirred under an nitrogen atmosphere with ice-bath cooling. After 0.5h, the solution was washed with 1N HCl, an aqueous solution of $NaHCO_3$ and brine and then dried over sodium sulphate, filtered, and evaporated. The residue was purified by flash chromatography eluting with dichloromethane/ethyl acetate (90/10) and crystallised from dichloromethane/ hexane to give the title compound as white crystals (2 g).

m.p.:157-159°C

$[\alpha]_D$ = + 46° (C=1.2 ; $CHCl_3$)

Analysis for $C_{29}H_{30}N_2O_2$: Calculated: C,79.42;H,6.89;N,6.39;

Found: C,78.99;H,7.01;N,6.31%.

Similarly prepared were:

Example 2

2-(3-Dimethylamino-4-methyl benzoyl)-N-(7-methyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide as white crystals, m.p.: 140-141°C

$[\alpha]_D$ = + 43.6° (C=1.2 ; $CHCl_3$)

Analysis for $C_{31}H_{35}N_3O_2$: Calculated: C,77.31;H,7.32;N,8.72;

Found: C,77.04;H,7.54;N,8.66%.

from N-(7-methyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (Intermediate 7) and 3-dimethylamino-4-methyl benzoic acid.

Example 3

2-(3-Dimethylamino benzoyl)-N-(7-methyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide as white crystals,

m.p.: 186-187°C

$[\alpha]_D$ = + 41° (C=0.4 ; $CHCl_3$)

Analysis for $C_{30}H_{33}N_3O_2$: Calculated: C,77.06;H,7.11;N,8.99;
Found: C,77.22;H,7.04;N,9.03%.

from N-(7-methyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (Intermediate 7) and 3-dimethylamino benzoic acid.

Example 4

2-(3-(Morpholin-4-yl)benzoyl)- N-(7-methyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide as a white solid,

m.p.: 96-101°C

$[\alpha]_D$ = + 33.6° (C=1 ; $CHCl_3$)

Analysis for $C_{32}H_{35}N_3O_3$: Calculated: C,75.41;H,6.92;N,8.24;
Found: C,75.69;H,7.19;N,7.99%

from N-(7-methyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (Intermediate 7) and 3-(morpholin-4-yl)benzoic acid.

Example 5

2-(3-(Morpholin-4-yl)benzoyl)- N-(7-methoxy-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide as white crystals,

m.p.: 124-126°C

$[\alpha]_D$ = + 23.9° (C=0.4 ; $CHCl_3$)

Analysis for $C_{32}H_{35}N_3O_4$: Calculated: C,73.12;H,6.71;N,7.99;
Found: C,73.32;H,7.13;N,8.05%

from N-(7-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (Intermediate 8) and 3-(morpholin-4-yl)benzoic acid.

Example 6

2-(3-Dimethylamino benzoyl)-N-(7-methoxy-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide as white crystals,

m.p.: 164-166°C

$[\alpha]_D$ = + 25.6° (C=0.5 ; $CHCl_3$)

Analysis for $C_{30}H_{33}N_3O_3$: Calculated: C,74.51;H,6.88;N,8.69;
Found: C,74.42;H,7.26;N,8.72%.

from N-(7-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (Intermediate 8) and 3-dimethylamino benzoic acid.

Example 7

2-[3-(2-Dimethylamino-ethoxy)-benzoyl]-N-(7-isopropyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

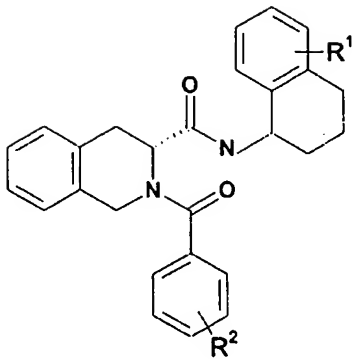
To a solution of N-(7-isopropyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (Intermediate 30) (2.84 g) in dichloromethane (100 mL) were added 3-(2-dimethylamino-ethoxy)-benzoic acid hydrochloride (2 g), 1-hydroxybenzotriazole (1.43 g) and triethylamine (1.89 g). The mixture was cooled at 0°C and treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2 g) followed by stirring for 16 hours at room temperature. The reaction mixture was diluted with dichloromethane and washed successively with water, an aqueous solution of NaHCO3 and brine, and then was dried over sodium sulfate, filtered and evaporated. The residue was purified by flash chromatography eluting with dichloromethane / methanol (96/4) and crystallised from diisopropyl ether to give the title compound as a white solid (3.2 g).

m.p.: 88-90°C

$[\alpha]_D$ = + 27.2° (C=1 ; $CHCl_3$)

Analysis for C34H41N3O3 : Calculated: C,75.66;H,7.66;N,7.79;
Found: C,75.21;H,7.85;N,7.71%.

Similarly prepared were:



Ex	R^1	R^2	molec formula: CHN Calc: CHN found: $[\alpha]_D$	m.p °C
8	7-methyl (from Intermediate 7)	3-(2-Dimethylamino-ethoxy)	C32H37N3O3 C,75.12;H,7.29;N,8.21 C,75.24;H,7.66;N,8.01 + 36° (C=0.3 ; $CHCl_3$)	59
9	5,7-dimethyl (from Intermediate 33)	3-(2-Dimethylamino-ethoxy)	C33H39N3O3 C,75.40;H,7.48;N,7.99 C,75.07;H,7.68;N,8.00 + 23.7° (C=0.5;$CHCl_3$)	67-69
10	7-isopropyl (from Intermediate 30)	4-Methyl	C31H34N2O2 C,79.80;H,7.34;N,6.00 C,79.36;H,6.92;N,5.98 + 35.6° (C=1 ;$CHCl_3$)	152-154
11	7-methyl (from Intermediate 7)	3,4-Methylenedioxy	C29H28N2O4 C,74.34;H,6.02;N,5.98 C,74.09;H,6.48;N,5.84 + 57.1° (C=0.4;$CHCl_3$)	93-95
12	7-isopropyl	3-Morpholin-4-yl	C34H39N3O3	93-95

	(from Intermediate 30)		C,75.95;H,7.31;N,7.81 C,75.44;H,7.33;N,7.97 + 26.5° (C=1 ; $CHCl_3$)	
13	7-isopropyl (from Intermediate 30)	3-(2-Diethylamino-ethoxy)	C36H45N3O3 C,76.16;H,7.99;N,7.40 C,75.88;H,8.00;N,7.47 + 25.4° (C=0.8;$CHCl_3$)	134-136
14	7-tert-butyl (from Intermediate 31)	3-Morpholin-4-yl-	C35H41N3O3 C,76.19;H,7.49;N,7.62 C,76.15;H,7.47;N,7.57 + 20.4° (C=0.5;$CHCl_3$)	169-171
15	7-tert-butyl (from Intermediate 31)	3-(2-Dimethylamino-ethoxy)	C35H44ClN3O3.HCl(2H2O) C,67.13;H,7.73;N,6.71 C,67.17;H,7.74;N,6.60 + 19.7° (C=0.7 ;$CHCl_3$)	119-121
16	7-isopropyl (from Intermediate 30)	3-(3-Dimethylamino-propoxy	C35H44ClN3O3.HCl(2H2O) C,67.13;H,7.73;N,6.71 C,67.26;H,7.88;N,6.72 + 24.9° (C=1.1 ;$CHCl_3$)	109-112
17	7-isopropyl (from Intermediate 30)	2-Diisopropylamino-ethoxy	C38H50ClN3O3.HCl(0.25H2O) C,69.70;H,8.08;N,6.42 C,69.88;H,8.11;N,6.37 + 23.6° (C=1 ; $CHCl_3$)	106-109
18	6,7-methylenedioxy (from Intermediate 35)	4-Methyl	C29H28N2O4 C,74.34;H,6.02;N,5.98	171-173

			C,74.13;H,6.43;N,5.73 + 31.6° (C=0.4 ;$CHCl_3$)	
19	6,7-methylenedioxy (from Intermediate 35)	3-Morpholin-4-yl	C32H33N3O5(0.25H2O) C,70.64;H,6.21;N,7.72 C,70.42;H,6.64;N,7.68 + 31.3° (C=0.4 ;$CHCl_3$)	117-119
20	5,7-dimethyl (from Intermediate 33)	4-Methyl	C30H32N2O2(0.4H2O) C,78.37;H,7.19;N,6.09 C,78.40;H,7.26;N,6.29 + 31° (C=1.1 ; $CHCl_3$)	146-147.5
21	6-fluoro-7-methoxy (from Intermediate 37)	4-Methyl	C29H29FN2O3 C,73.71;H,6.19;N,5.93 C,73.52;H,6.40;N,5.92 + 24.4° (C=0.4 ;$CHCl_3$)	176-178
22	7-methyl (from Intermediate 7)	3-Methoxy	C29H30N2O3(0.25H2O) C,75.87;H,6.70;N,6.10 C,75.79;H,6.69;N,6.07 + 34.1° (C=0.5 ;$CHCl_3$)	77-79
23	7-methoxy (from Intermediate 8)	3-(4-methyl-piperazin-1-yl)	C33H38N4O3(0.5H2O) C,72.37;H,7.18;N,10.23 C,72.17;H,7.24;N,10.04 + 25.3	107-109
24	7-methyl (from Intermediate 7)	3-Dimethylamino-4-methoxy	C31H35N3O3 C,74.82;H,7.09;N,8.44 C,75.02;H,7.12;N,8.43 + 50.3° (C=1.1; $CHCl_3$)	172-173
25	7-methyl	4-Chloro	C28H27ClN2O2	93-95

	(from Intermediate 7)		C,73.27;H,5.93;N,6.10 C,73.13;H,6.22;N,6.04 + 43.3° (C=1.1; $CHCl_3$)	
26	H (from Intermediate 32)	3-Morpholin-4-yl	C31H33N3O3 C,75.13;H,6.71;N,8.48 C,74.72;H,6.81;N,8.45 + 25.8° (C=0.5; $CHCl_3$)	98-100
27	H(from Intermediate 32)	2-Dimethylamino	C29H31N3O2 C,76.79;H,6.89;N,9.26 C,76.60;H,7.05;N,9.15 + 7.9° (C=0.8 MeOH)	129-131
28	7-isopropyl (from Intermediate 52)	3-(2-dimethylamino-propoxy)	C35H43N3O3.HCl(0.75H2O) C,69.63 ;H,7.60 ;N,6.96 C,69.65 ;H,7.26 ;N,6.74 +25.8°(C=0.7 ;CHCl3)	134-136
29	7-isopropyl (from Intermediate 53)	3-(2-dimethylamino-1-methyl-ethoxy)	C35H43N3O3.HCl(2H2O) C,73.25 ;H,8.11 ;N,7.12 C,73.32 ;H,8.16 ;N,7.08 +28.8° (C=0.6 ;CHCl3)	136-138
30	7-isopropyl (from Intermediate 54)	3-(2-dimethylamino-2-methyl-propoxy)	C36H45N3O3(1.25H2O) C,73.25 ;H,8.11 ;N,7.12 C,73.32 ;H,8.16 ;N,7.08 +28.8° (C=0.6 ;CHCl3)	129-131
31	7-isopropyl (from Intermediate 55)	3-(2-dimethylamino-1,1-dimethyl-ethoxy)	C36H45N3O3.HCl.2H2O C,67.53 ;H,7.87 ;N,6.56 C,67.46 ;H,8.20 ;N,6.89	114

			+18° (C=0.7 ;CHCl3)	

Example 32

2-(3-Morpholin-4-yl-benzoyl)-N-(4,4,7-trimethyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide isomer 1 and isomer 2.

To a solution of (R)-2-(3-morpholin-4-yl-benzoyl)-1,2,3,4-tetrahydro isoquinoline-3-carboxylic acid (0.33 g) in dichloromethane (10 mL) were added racemic 4,4,7-trimethyl-1,2,3,4-tetrahydro-naphthalen-1-ylamine hydrochloride (0.22 g), 1-hydroxy benzotriazole (0.17 g) and triethylamine (0.23 g). The mixture was cooled to 0°C and treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.25 g) followed by stirring for 3 hours at room temperature. The reaction mixture was washed successively with water, 1N HCl, an aqueous solution of NaHCO3 and brine, and then was dried over sodium sulfate, filtered and evaporated. The residue was purified by flash chromatography eluting with dichloromethane/methanol (99/1) to give the title compound

Isomer 1 as a white solid (0.12 g),

m.p.: 113-115°C

$[\alpha]_D$ = + 20° (C=0.4 ; $CHCl_3$)

Analysis for C34H39N3O3 : Calculated: C,75.95;H,7.31;N,7.81;

Found: C,75.80;H,7.59;N,7.61%.

followed by

Example 33 Isomer 2 as a white solid (0.08 g),

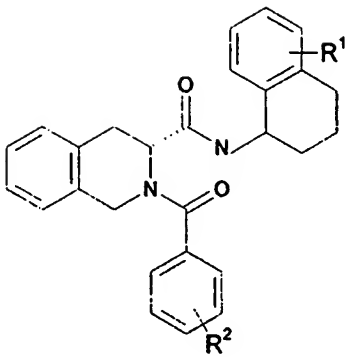
m.p.: 117-119°C

$[\alpha]_D$ = + 25.4° (C=0.4 ; $CHCl_3$)

Analysis for C34H39N3O3 : Calculated: C,75.95;H,7.31;N,7.81;

Found: C,75.47;H,7.23;N,7.87%.

Similarly prepared were :



Ex	R^1	R^2	molec formula: CHN Calc: CHN found: $[\alpha]_D$	m.p °C
34	4,4,6-trimethyl (isomer 1)	3-morpholin-4-yl-	C34H39N3O3 C,75.95;H,7.31;N,7.81 C,76.33;H,7.56;N,7.74 + 17.5° (C=0.4; $CHCl_3$)	116-118
35	4,4,6-trimethyl (isomer 2)	3-morpholin-4-yl-	C34H39N3O3 C,75.95;H,7.31;N,7.81 C,76.33;H,7.56;N,7.74 + 43.6° (C=0.4; $CHCl_3$)	112-114
36	7-methoxy-4,4-dimethyl (isomer 1)	3-morpholin-4-yl-	C34H39N3O4 C,73.75;H,7.10;N,7.59 C,73.65;H,7.47;N,7.38 + 12.2° (C=0.4; $CHCl_3$)	97-99
37	7-methoxy-4,4-dimethyl (isomer 2)	3-morpholin-4-yl-	C34H39N3O4 C,73.75;H,7.10;N,7.59 C,73.55;H,7.44;N,7.30 + 17° (C=0.5; $CHCl_3$)	93-95

38	3,3-dimethyl (isomer 1)	3-morpholin-4-yl-	C33H37N3O3 C,75.69;H,7.12;N,8.02 C,75.76;H,7.57;N,7.79 + 33.5° (C=0.5; $CHCl_3$)	118-120
39	3,3-dimethyl (isomer 2)	3-morpholin-4-yl-	C33H37N3O3 C,75.69;H,7.12;N,8.02 C,75.71;H,7.43;N,7.84 + 16° (C=1; $CHCl_3$)	120-122
40	7-methoxy-4,4-dimethyl (isomer 1)	3-dimethylamino	C32H37N3O3 C,75.12;H,7.29;N,8.21 C,75.03;H,7.43;N,8.12 + 13.4° (C=0.5; $CHCl_3$)	174-176
41	7-methoxy-4,4-dimethyl (isomer 2)	3-dimethylamino	C32H37N3O3 C,75.12;H,7.29;N,8.21; C,74.57;H,7.75;N,8.02 + 12.6° (C=0.4; $CHCl_3$)	97-99
42	5,7-di-Me (isomer 1)	3-morpholin-4-yl	C33H37N3O3 C,75.69;H,7.12;N,8.02; C,75.60;H,7.35;N,7.86 + 28° (C=0.4; $CHCl_3$)	183-185
43	5,7-di-Me (isomer 2)	3-morpholin-4-yl	C33H37N3O3 C,75.69;H,7.12;N,8.02; C,75.99;H,7.62;N,7.85 + 33.7° (C=0.6; $CHCl_3$)	96-98
44	7- trifluoromethoxy (mixture of isomer 1 and 2)	3-morpholin-4-yl	C32H32F3N3O4 C,66.31;H,5.56;N,7.25 C,66.37;H,5.83;N,7.18	102-107

45	7-fluoro (mixture of isomer 1 and 2)	3-morpholin-4-yl	C31H32FN3O3 C,72.49;H,6.28;N,8.18 C,72.34;H,6.21;N,8.13	145-150

Biological Assay

HepG2 cells were seeded at 30 000 cells/well in 96 well plates. After 4 days, confluent cells were incubated with compounds for 24 hours in RPMI medium containing 1% FCS and 50 µCi/ml 35S-methionine. Compounds were dissolved in DMSO and tested onto cells from 5 µM to 0.32 nM. Production of radiolabeled apoB-100 and apoA-1 (used as a selectivity control) was quantified by analysis of supernatants using SDS PAGE and exposure of gels onto PhosphorImager screens. Inhibition of apoB-100 and apoA-1 secretion by compounds was calculted taking untreated cells as controsl, and IC50 of each compound was determined on both apoproteins.

Biological Results

The following table illustrates the activity of the compounds of the invention in the assay described above:

Ex	Inhibition of apoB-100 IC50 (nM)	Inhibition of apoA-1 IC50 (nM)
1	0.9	> 5000
7	1	> 5000
11	2	> 5000
12	0.7	> 5000
13	6	> 5000
17	10	> 5000
18	10	> 5000

Tablet compositions

The following compositions A and B can be prepared by wet granulation of ingredients (a) to (c) and (a) to (d) with a solution of povidone, followed by addition of the magnesium stearate and compression.

Composition A

		mg/tablet	mg/tablet
(a)	Active ingredient	250	250
(b)	Lactose B.P.	210	26
(c)	Sodium Starch Glycollate	20	12
(d)	Povidone B.P.	15	9
(e)	Magnesium Stearate	5	3
		500	300

Composition B

		mg/tablet	mg/tablet
(a)	Active ingredient	250	250
(b)	Lactose 150	150	-
(c)	Avicel PH 101	60	26
(d)	Sodium Starch Glycollate	20	12
(e)	Povidone B.P.	15	9
(f)	Magnesium Stearate	5	3
		500	300

Composition C

	mg/tablet
Active ingredient	100
Lactose	200
Starch	50
Povidone	5
Magnesium Stearate	4
	359

The following compositions D and E can be prepared by direct compression of the admixed ingredients. The lactose used in composition E is of the direct

compression type.

Composition D

	mg/tablet
Active ingredient	250
Magnesium Stearate	4
Pregelatinised Starch NF15	146
	400

Composition E

	mg/tablet
Active ingredient	250
Magnesium Stearate	5
Lactose	145
Avicel	100
	500

Composition F (Controlled release composition)

		mg/tablet
(a)	Active ingredient	500
(b)	Hydroxypropylmethylcellulose (Methocel K4M Premium)	112
(c)	Lactose B.P.	53
(d)	Povidone B.P.C.	28
(e)	Magnesium Stearate	7
		700

The composition can be prepared by wet granulation of ingredients (a) to (c) with a solution of povidone, followed by addition of the magnesium stearate and compression.

Composition G (Enteric-coated tablet)

Enteric-coated tablets of Composition C can be prepared by coating the tablets with 25mg/tablet of an enteric polymer such as cellulose acetate phthalate,

polyvinylacetate phthalate, hydroxypropylmethyl- cellulose phthalate, or anionic polymers of methacrylic acid and methacrylic acid methyl ester (Eudragit L). Except for Eudragit L, these polymers should also include 10% (by weight of the quantity of polymer used) of a plasticizer to prevent membrane cracking during application or on storage. Suitable plasticizers include diethyl phthalate, tributyl citrate and triacetin.

Composition H (Enteric-coated controlled release tablet)

Enteric-coated tablets of Composition F can be prepared by coating the tablets with 50mg/tablet of an enteric polymer such as cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropylmethyl- cellulose phthalate, or anionic polymers of methacrylic acid and methacrylic acid methyl ester (Eudragit L). Except for Eudragit L, these polymers should also include 10% (by weight of the quantity of polymer used) of a plasticizer to prevent membrane cracking during application or on storage. Suitable plasticizers include diethyl phthalate, tributyl citrate and triacetin.

(ii) Capsule compositions

Composition A

Capsules can be prepared by admixing the ingredients of Composition D above and filling two-part hard gelatin capsules with the resulting mixture. Composition B (infra) may be prepared in a similar manner.

Composition B

		mg/capsule
(a)	Active ingredient	250
(b)	Lactose B.P.	143
(c)	Sodium Starch Glycollate	25
(d)	Magnesium Stearate	2
		420

Composition C

		mg/capsule
(a)	Active ingredient	250

(b)	Macrogol 4000 BP	350
		600

Capsules can be prepared by melting the Macrogol 4000 BP, dispersing the active ingredient in the melt and filling two-part hard gelatin capsules therewith.

Composition D

	mg/capsule
Active ingredient	250
Lecithin	100
Arachis Oil	100
	450

Capsules can be prepared by dispersing the active ingredient in the lecithin and arachis oil and filling soft, elastic gelatin capsules with the dispersion.

Composition E (Controlled release capsule)

		mg/capsule
(a)	Active ingredient	250
(b)	Microcrystalline Cellulose	125
(c)	Lactose BP	125
(d)	Ethyl Cellulose	13
		513

The controlled release capsule composition can be prepared by extruding mixed ingredients (a) to (c) using an extruder, then spheronising and drying the extrudate. The dried pellets are coated with a release controlling membrane (d) and filled into two-part, hard gelatin capsules.

Composition F (Enteric capsule)

		mg/capsule
(a)	Active ingredient	250
(b)	Microcrystalline Cellulose	125
(c)	Lactose BP	125

(d)	Cellulose Acetate Phthalate	50
(e)	Diethyl Phthalate	5
		555

The enteric capsule composition can be prepared by extruding mixed ingredients (a) to (c) using an extruder, then spheronising and drying the extrudate. The dried pellets are coated with an enteric membrane (d) containing a plasticizer (e) and filled into two-part, hard gelatin capsules.

Composition G (Enteric-coated controlled release capsule)

Enteric capsules of Composition E can be prepared by coating the controlled-release pellets with 50mg/capsule of an enteric polymer such as cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropylmethylcellulose phthalate, or anionic polymers of methacrylic acid and methacrylic acid methyl ester (Eudragit L). Except for Eudragit L, these polymers should also include 10% (by weight of the quantity of polymer used) of a plasticizer to prevent membrane cracking during application or on storage. Suitable plasticizers include diethyl phthalate, tributyl citrate and triacetin.

(iii) Intravenous injection composition

Active ingredient	0.200g
Sterile, pyrogen-free phosphate buffer (pH 9.0) to	10 ml

The active ingredient is dissolved in most of the phosphate buffer at 35-40^{o}C, then made up to volume and filtered through a sterile micropore filter into sterile 10 ml glass vials (Type 1) which are sealed with sterile closures and overseals.

(iv) Intramuscular injection composition

Active ingredient	0.20 g
Benzyl Alcohol	0.10 g
Glycofurol 75	1.45 g
Water for Injection q.s. to	3.00 ml

The active ingredient is dissolved in the glycofurol. The benzyl alcohol is then added and dissolved, and water added to 3 ml. The mixture is then filtered through a sterile micropore filter and sealed in sterile 3 ml glass vials (Type 1).

(v) Syrup composition

Active ingredient	0.25g
Sorbitol Solution	1.50g
Glycerol	1.00g
Sodium Benzoate	0.005g
Flavour	0.0125ml
Purified Water q.s. to	5.0ml

The sodium benzoate is dissolved in a portion of the purified water and the sorbitol solution added. The active ingredient is added and dissolved. The resulting solution is mixed with the glycerol and then made up to the required volume with the purified water.

(vi) Suppository composition

	mg/suppository
Active ingredient	250
Hard Fat, BP (Witepsol H15 - Dynamit NoBel)	1770
	2020

One-fifth of the Witepsol H15 is melted in a steam-jacketed pan at 45°C maximum. The active ingredient is sifted through a 200lm sieve and added to the molten base with mixing, using a Silverson fitted with a cutting head, until a smooth dispersion is achieved. Maintaining the mixture at 45°C, the remaining Witepsol H15 is added to the suspension which is stirred to ensure a homogenous mix. The entire suspension is then passed through a 250lm stainless steel screen and, with continuous stirring, allowed to cool to 40°C. At a temperature of 38-40°C, 2.02g aliquots of the mixture are filled into suitable

plastic moulds and the suppositories allowed to cool to room temperature.

(vii) Pessary composition

	mg/pessary
Active ingredient (63lm)	250
Anhydrous Dextrose	380
Potato Starch	363
Magnesium Stearate	7
	1000

The above ingredients are mixed directly and pessaries prepared by compression of the resulting mixture.

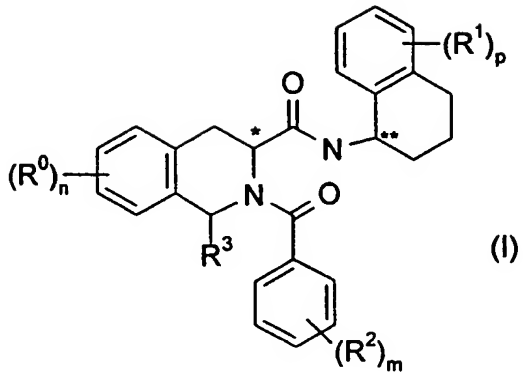
(viii) Transdermal composition

Active ingredient	200mg
Alcohol USP	0.1ml
Hydroxyethyl cellulose	

The active ingredient and alcohol USP are gelled with hydroxyethyl cellulose and packed in a transdermal device with a surface area of 10 cm^2.

Claims

1. A compound of formula (I)



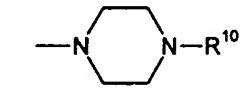
(I)

wherein

R^0 represents hydrogen, halogen, C_{1-4}alkyl, C_{1-4}alkoxy or a methylenedioxy group, and n represents an integer from 1-4;

R^1 represents hydrogen, halogen, C_{1-4}alkyl, C_{1-4}alkoxy, trifluoromethoxy or a methylenedioxy group, and p represents an integer from 1-4;

R^2 represents one or more groups selected from hydrogen, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, a methylenedioxy group,NR^4R^5, -(C_{1-4}alkylene)-NR^6R^7, -NR^4- or -O-(C_{1-4} alkylene)-NR^8R^9, 4-morpholino,

or  , and m represents an integer from 1-4;

R^3 represents hydrogen or C_{1-4} alkyl;

R^4-R^{10} independently represent hydrogen or C_{1-4} alkyl;

or a pharmaceutically acceptable salt or solvate thereof.

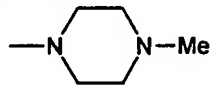
2. A compound as claimed in claim 1 wherein R^0 is hydrogen.

3. A compound according to Claim 1 or Claim 2 where R^1 hydrogen, C_{1-4} alkyl, halogen, methoxy, or trifluoromethoxy, p is 1, 2 or 3, and R^1 is substituted on any one, two or three of the 3-, 4-, 5-, 6- , 7- and 8- positions of the bicyclic ring, including gem substitution.

4. A compound as claimed in any one of claims 1 to 3 where R^1 is isopropyl

substituted in the 7- position of the bicyclic ring.

5. A compound as claimed in any one of claims 1 to 4 where R^2 is hydrogen, C_{1-4} alkyl, halogen, methoxy, methylenedioxy, NMe_2, -O-(C_{1-4} alkylene)-NMe_2, 4-morpholino

or 

, and m is suitably 1, 2 or 3.

6. A compound as claimed in any one of claims 1 to 5 wherein R^2 is 2-dimethylamino-ethoxy substituted in the 3-position of the phenyl ring.

7. A compound as claimed in any one of claims 1 to 6 wherein R^3 is hydrogen.

8. A compound selected from:
2-(4-Methyl benzoyl)-N-(7-methyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-(3-Dimethylamino-4-methyl benzoyl)-N-(7-methyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-(3-Dimethylamino benzoyl)-N-(7-methyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-(3-(Morpholin-4-yl)benzoyl)- N-(7-methyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-(3-(Morpholin-4-yl)benzoyl)-N-(7-methoxy-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-(3-Dimethylamino benzoyl)-N-(7-methoxy-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-[3-(2-Dimethylamino-ethoxy)-benzoyl]-N-(7-isopropyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-[3-(2-Dimethylamino-ethoxy)-benzoyl]-N-(7-methyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-[3-(2-Dimethylamino-ethoxy)-benzoyl]-N-(5,7-dimethyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-(4-Methyl-benzoyl)-N-(7-isopropyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;

2-(3,4-Methylenedioxy-benzoyl)-N-(7-methyl-1,2,3,4-tetrahydro-naphthalen -1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-(3-Morpholin-4-yl-benzoyl)-N-(7-isopropyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-[3-(2-Diethylamino-ethoxy)-benzoyl]-N-(7-isopropyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-(3-Morpholin-4-yl-benzoyl)-N-(7-tert-butyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-[3-(2-Dimethylamino-ethoxy)-benzoyl]-N-(7-tert-butyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-[3-(3-Dimethylamino-propoxy)-benzoyl]-N-(7-isopropyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-[3-(2-Diisopropylamino-ethoxy)-benzoyl]-N-(7-isopropyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-(4-Methyl-benzoyl)-N-(6,7-methylenedioxy-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-(3-Morpholin-4-yl-benzoyl)-N-(6,7-methylenedioxy-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-(4-Methyl-benzoyl)-N-(5,7-dimethyl-1,2,3,4-tetrahydro-naphthalen -1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-(4-Methyl-benzoyl)-N-(6-fluoro-7-methoxy-1,2,3,4-tetrahydro-naphthalen -1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-(3-Methoxy-benzoyl)-N-(7-methyl-1,2,3,4-tetrahydro-naphthalen -1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-[3-(4-Methyl-piperazin-1-yl)-benzoyl]-N-(7-methoxy-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-(3-Dimethylamino-4-methoxy-benzoyl)-N-(7-methyl-1,2,3,4-tetrahydro-naphthalen -1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-(4-Chloro-benzoyl)-N-(7-methyl-1,2,3,4-tetrahydro-naphthalen -1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-(3-Morpholin-4-yl-benzoyl)-N-(1,2,3,4-tetrahydro-naphthalen -1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-(2-Dimethylamino-benzoyl)-N-(1,2,3,4-tetrahydro-naphthalen -1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;

2-(3-Morpholin-4-yl-benzoyl)-N-(4,4,7-trimethyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide isomer 1;
2-(3-Morpholin-4-yl-benzoyl)-N-(4,4,7-trimethyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide isomer 2;
2-(3-Morpholin-4-yl-benzoyl)-N-(4,4,6-trimethyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide isomer 1;
2-(3-Morpholin-4-yl-benzoyl)-N-(4,4,6-trimethyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide isomer 2;
2-(3-Morpholin-4-yl-benzoyl)-N-(7-methoxy-4,4-dimethyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide isomer 1;
2-(3-Morpholin-4-yl-benzoyl)-N-(7-methoxy-4,4-dimethyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide isomer 2;
2-(3-Morpholin-4-yl-benzoyl)-N-(3,3-dimethyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide isomer 1;
2-(3-Morpholin-4-yl-benzoyl)-N-(3,3-dimethyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide isomer 2;
2-(3-Dimethylamino-benzoyl)-N-(7-methoxy-4,4-dimethyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide isomer 1;
2-(3-Dimethylamino-benzoyl)-N-(7-methoxy-4,4-dimethyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide isomer 2;
2-(3-Morpholin-4-yl-benzoyl)-N-(5,7-dimethyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide isomer 1;
2-(3-Morpholin-4-yl-benzoyl)-N-(5,7-dimethyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide isomer 2;
2-(3-Morpholin-4-yl-benzoyl)-N-(7-trifluoromethoxy-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-(3-Morpholin-4-yl-benzoyl)-N-(7-fluoro-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-[3-(2-dimethylamino-propoxy)-benzoyl]-N-(7-isopropyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-[3-(2-dimethylamino-1-methyl-ethoxy))-benzoyl]-N-(7-isopropyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
2-[3-(2-dimethylamino-2-methyl-propoxy))-benzoyl]-N-(7-isopropyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;

2-[3-(2-dimethylamino-1,1-dimethyl-ethoxy))-benzoyl]-N-(7-isopropyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
or a pharmaceutically acceptable salt or solvate thereof.

9. 2-[3-(2-Dimethylamino-ethoxy)-benzoyl]-N-(7-isopropyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;
or a pharmaceutically acceptable salt or solvate thereof.

10. A compound according to any one of Claims 1 to 9 for use in therapy.

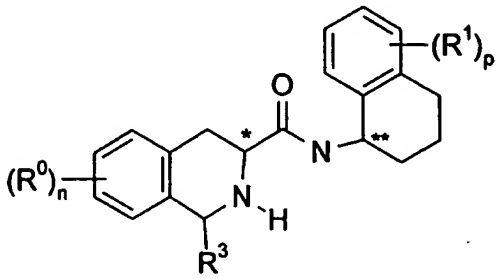
11. A method for the treatment of a mammal, including man, of conditions resulting from elevated circulating levels of apoB-100 comprising administration of an effective amount of a compound according to any one of claims 1 to 9 or a pharmaceutically acceptable derivative thereof.

12. The use of a compound according to any one of claims 1 to 9 or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for use in the treatment of conditions resulting from elevated circulating levels of apoB-100.

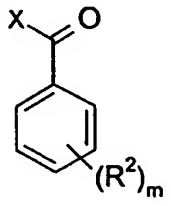
13. A pharmaceutical composition comprising a compound according to any one of claims 1 to 9 or a pharmaceutically acceptable derivative thereof, together with one or more pharmaceutically acceptable carriers.

14. A process for preparing a compound of formula (I) as claimed in claim 1 which comprises:

(a) reacting a compound of formula (II) with a compound of formula (III)



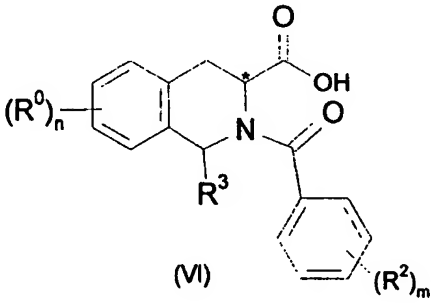
(II)



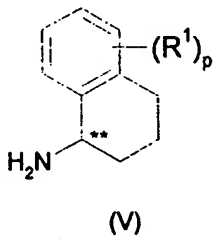
(III)

where X represents a suitable halide leaving group or X represents a hydroxy group, or

(b) by reaction of compounds of formula (VI) and compounds of formula (V)



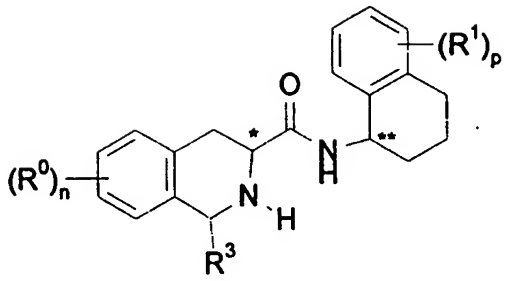
(VI)



(V)

under standard conditions for amine and acid couplings.

15. An intermediate represented by formula (II)



(II)

wherein

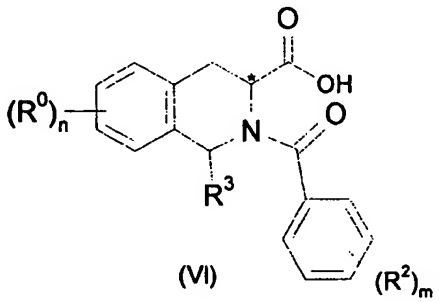
R^0 represents hydrogen, halogen, C_{1-4}alkyl, C_{1-4}alkoxy or a methylenedioxy group, and n represents an integer from 1-4;

R^1 represents hydrogen, halogen, C_{1-4}alkyl, C_{1-4}alkoxy, trifluoromethoxy or a methylenedioxy group, and p represents an integer from 1-4;

R^3 represents hydrogen or C_{1-4} alkyl;

or a pharmaceutically acceptable salt or solvate thereof.

16. An intermediate represented by formula (VI)

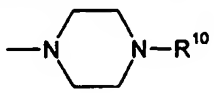


(VI)

wherein

R^0 represents hydrogen, halogen, C_{1-4}alkyl, C_{1-4}alkoxy or a methylenedioxy group, and n represents an integer from 1-4;

R^2 represents one or more groups selected from hydrogen, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, a methylenedioxy group,NR^4R^5, -(C_{1-4}alkylene)-NR^6R^7, N or -O-(C_{1-4} alkylene)-NR^8R^9, 4-morpholino,

or  , and m represents an integer from 1-4;

R^3 represents hydrogen or C_{1-4} alkyl;
R^4-R^{10} independently represent hydrogen or C_{1-4} alkyl;
or a pharmaceutically acceptable salt or solvate thereof.

INTERNATIONAL SEARCH REPORT

Internat. al Application No
PCT/EP 98/02244

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D217/26 A61K31/47 C07D405/06 C07D405/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 12611 A (JAPAT LTD.;SWITZ.) 11 May 1995 see page 72; example 88, the first paragraph therein ---	16
X	SHINKAI H ET AL: "N-Acylphenylalanines and related compounds. A new class of oral hypoglycemic agents" J. MED. CHEM. , vol. 31, no. 11, 1988, pages 2092-2097, XP000670266 see page 2093; column 2, scheme I, the compounds no. 6 and 7 ---	16
X	EP 0 161 102 A (GLAXO GROUP LTD.;UK) 13 November 1985 see page 12, line 4 - line 5 --- -/--	16

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 August 1998	28. 08. 98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fink, D

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Interna al Application No
PCT/EP 98/02244

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 134 582 A (TANABE SEIYAKU CO., LTD.;JAPAN) 20 March 1985 see pages 39-40; preparation 6, step (b) ---	16
A	WO 96 40640 A (PFIZER ;CHANG GEORGE (US); DORFF PETER H (US); QUALLICH GEORGE J () 19 December 1996 see the whole document; in particular page 35, lines 31-33 and page 1, lines 4-7 ---	1-16
P,X	EP 0 803 505 A (ADIR ET COMPAGNIE;FR.) 29 October 1997 see page 15; example 10, "Stade A" -----	16

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 98/02244

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 11
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 11 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interna al Application No
PCT/EP 98/02244

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9512611 A	11-05-1995	AU 691201 B	14-05-1998
		AU 7856594 A	23-05-1995
		BR 9407933 A	26-11-1996
		CA 2173875 A	11-05-1995
		EP 0728145 A	28-08-1996
		FI 961804 A	30-04-1996
		NO 961725 A	29-04-1996
		US 5780498 A	14-07-1998
		ZA 9408541 A	02-05-1995
EP 0161102 A	13-11-1985	AU 587184 B	10-08-1989
		AU 4196585 A	07-11-1985
		CA 1268178 A	24-04-1990
		DK 196885 A,B,	04-11-1985
		JP 61010582 A	18-01-1986
		US 4835158 A	30-05-1989
EP 0134582 A	20-03-1985	GB 2146026 A	11-04-1985
		JP 61010596 A	18-01-1986
		US 4563306 A	07-01-1986
WO 9640640 A	19-12-1996	AU 5478496 A	19-12-1996
		BG 100637 A	31-03-1997
		CN 1141918 A	05-02-1997
		CZ 9601644 A	15-01-1997
		EP 0832069 A	01-04-1998
		FI 974440 A	27-01-1998
		LV 11615 A	20-12-1996
		LV 11615 B	20-04-1997
		NO 962385 A	09-12-1996
		PL 314636 A	09-12-1996
		SG 44952 A	19-12-1997
		SI 9600183 A	30-04-1997
		SK 72696 A	05-11-1997
EP 0803505 A	29-10-1997	FR 2748026 A	31-10-1997
		AU 1912197 A	30-10-1997
		CA 2203618 A	26-10-1997
		CN 1165817 A	26-11-1997
		JP 10059936 A	03-03-1998

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. ial Application No
PCT/EP 98/02244

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0803505 A		NO 971862 A	27-10-1997
		PL 319684 A	27-10-1997